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Ischemic nephropathy: Detection and therapeutic intervention

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Ischemic nephropathy: Detection and therapeutic intervention. Although the real prevalence of ischemic nephropathy as a cause of end-stage renal disease is unknown, its incidence has increased in past years. The diagnosis of this pathology requires that a number of functional and anatomic tests be carried out. The initial approach should be to perform duplex Doppler ultrasonography which, besides providing data on the size and extent of the stenosis, enables the intrarenal resistive index to be estimated to determine the pattern of renal parenchyma injury and the expected progression if revascularized.

The most frequently used morphologic techniques are magnetic resonance angiography and computer tomography angiography. In the event of ischemic neuropathy, it is necessary to perform a renal arteriography regardless of the inherent risks of contrast toxicity or atheroembolism.

Various therapeutic options are reviewed, with emphasis on percutaneous transluminal renal angiography plus stent as the first indication. Even though initial reports were contradictory, several meta-analyses have concluded that better blood pressure control and renal function improvement are achieved with percutaneous transluminal renal angiography plus stent than with conventional medical therapy. Surgical revascularization is preferable in patients with severe aorto-iliac pathology and renal artery ostium complete thrombosis. The risks and benefits of these procedures must be evaluated on an individual basis.

Ischemic nephropathy (IN) can be defined as a significant reduction in glomerular filtration rate (GFR) in patients with hemodynamically significant renovascular occlusive disease (RVD) affecting the entire functional renal parenchyma. This clinical entity has been described by various authors as ischemic renal disease, chronic renal ischemic disease, azotemic RVD, atherosclerotic RVD, or renal insufficiency of renovascular hypertension [1].

The prevalence of IN has not been precisely established, but various autopsy-related studies have reported a prevalence of 18% among patients aged 64 to 75 years and 42% among patients older than 75 years. Thus, the prevalence of IN seems to depend on the age of the population, increasing at greater ages. Disease prevalence among those presenting for angiography ranged from 11% to 42%, with the greatest prevalence in those with generalized atherosclerosis, peripheral vascular disease, and aortic atherosclerotic disease [2, 3]. Chronic renal failure due to ischemic RVD is a potentially reversible disorder. Progressive renal artery stenosis that threatens the entire renal mass, potentially resulting in renal insufficiency or end-stage renal disease (ESRD), is usually defined as significant high-grade stenosis of both renal arteries or as stenosis of a single kidney. It has been estimated that it may be responsible for 5% to 22% of cases of advanced renal failure in patients who are older than 50 years [4]. In one study, IN was diagnosed as the primary cause of ESRD in patients older than 65 years. In another series of bilateral RVD, 12% of cases progressed to ESRD and had an average decline in GFR of 8 mL/min/year [5].

Fatica et al reported that the incidence of ESRD caused by IN was increasing at an annual rate of 12.4% for RVD-ESRD over the study period, which was greater than that of diabetes mellitus-ESRD (8.4%) or all-cause ESRD (5.4%) [6]. Clinical findings associated with the presence of RVD are hypertension, advanced age, renal insufficiency, extrarenal atherosclerosis, renal artery or abdominal bruit, diabetes mellitus, congestive heart failure symptoms, female sex, and smoking.

A multicenter study conducted by the Spanish Group of Ischemic Nephrology (GEDENI) [7], which involved 20 Spanish hospitals, reported a mean age of 68.7 years and a predominance of men (78.3%) among 156 IN patients. Most of them were hypertensive (97.4%), smoking (69.8%), and hypercholesterolemic (62.9%). Isolated or associated atherosclerosis in other vascular beds was present in 82% of patients, peripheral arteriopathy was observed in more than 65% of patients, and associated arteriopathy or ischemic cardiomyopathy was observed in 21.6% of patients.

Renal insufficiency and hypertension are the predominant clinical features of IN. However, according to a report published by Alcazar et al, 29.5% of patients developed acute renal failure (ARF) as the IN presentation; in 12 patients (57%), it was secondary to angiotensin-converting enzyme inhibitor (ACE-I) treatment, and in 28.5% of patients, it was due to renal artery occlusion [8]. The kidney can develop collateral circulation at the

Key words: ischemic nephropathy, ischemic renal disease, renovascular disease, atherosclerotic renal artery disease, percutaneous transluminal renal angioplasty.

expense of the lumbar, urethral, and suprarenal arteries. Therefore, the kidney may survive despite a very low filtration pressure and GFR.

In another series [9, 10], it was reported that 6% to 38% of patients with severe RVD develop ARF when treated with ACE-I. Similarly, angiotensin II receptor antagonists (AIIRA) may produce the same hemodynamic disorder as ACE-I and thus precipitate ARF [9, 10].

DIAGNOSTIC APPROACH

Because there are several clinical signs that suggest a diagnosis of IN, it is important to perform a complete anamnesis and physical examination. Signs and symptoms that indicate IN are: sudden onset of hypertension, especially in young patients and particularly in women; the presence of severe hypertension with signs of atherosclerosis in other vascular territories in men older than 60 years; hypertension and vascular bruit; grade III retinopathy in 25% to 40% of patients; elevation of serum creatinine levels after administration of ACE-I or AIIRA; episodes of cardiac failure and acute pulmonary edema; and hypertension refractory to treatment with drugs other than antihypertensive drugs.

However, the diagnosis should rely on imaging studies to enhance the specificity of clinical findings. Ideally, the screening test should be readily available, noninvasive, non-nephrotoxic, and should provide an anatomic diagnosis of IN as well as an indication of its functional significance. In addition, it should also provide information on which patients are likely to benefit from intervention [11].

The gold standard for diagnosing renal artery stenosis is renal arteriography. However, several less-invasive tests have been evaluated for screening purposes. False-negative tests (low sensitivity) are the major concern with all noninvasive tests, because patients with a potentially correctable cause of hypertension may be overlooked.

Duplex doppler ultrasonography

In centers that have used duplex Doppler ultrasonography for some time, the sensitivity and specificity of this test were reported to be greater than 96% when both intrarenal and extrarenal arterial analyses were combined. Its most significant limitation relates to localization of the renal arteries. The limitation depends on the degree of abdominal obesity, intestinal gas content, experience and patience of the observer, and time spent performing the examination; thus, it has been criticized as observer dependent.

Duplex Doppler ultrasound enables calculation of a resistive index, of a measure of the integrity of small vessel circulation, and of parenchymal injury. A resistive index value greater than 0.80 for the kidney contralateral to a stenosis indicates severe parenchymal disease, a small likelihood of clinical benefit from blood pressure control, and renal function recovery from revascularization. The resistive index is decreased in stenotic kidneys because of waveform dampening, and therefore lower values may not reflect preserved parenchyma. However, a resistive index greater than 0.80 in a stenotic kidney indicates that severe parenchymal disease is likely and that there will be a poor clinical response to revascularization. For these reasons, duplex Doppler ultrasound is an appropriate initial screening test when expertise is available [12].

Renal scintigraphy

Currently, this technique is used only to demonstrate renal feasibility in patients with nonfunctioning kidneys.

Magnetic resonance angiography

Magnetic resonance angiography (MRA) is a noninvasive test that involves the administration of gadolinium, a non-nephrotoxic contrast agent. In centers where reliable duplex Doppler testing is unavailable, gadolinium-enhanced MRA is likely to be the screening test of choice. The main problems with MRA are its tendency to overestimate the severity of the stenosis and its degree of interobserver variability. The use of gadolinium-enhanced three-dimensional MRA improves the specificity of the examination. For diagnosis of atherosclerotic renal artery stenosis >50%, the sensitivity and specificity of gadolinium-enhanced MRA are 97% and 93%, respectively, and 94% and 85% for non-enhanced MRA. Combination of the MRA with cardiac-gated phase contrast flow measurements can facilitate assessment of the hemodynamic significance of a stenosis. Use of the combined protocol may permit a more accurate assessment of the degree of stenosis and reduce interobserver variability. Recently, combined MRA and phase contrast magnetic resonance have shown promise for estimating the functional significance of a stenosis from the renal artery differential pressure across the stenosis [13]. These new techniques are currently under study and are therefore not routinely used in many centers. To date, MRA procedures have not proven useful in predicting clinical responses to revascularization.

Spiral computed tomographic angiography

The sensitivity of this method varies from 67% to 92% [27]. It can be improved to 98%, with a specificity of 84%, by using maximum-intensity projections and three-dimensional techniques. The need to administer 100 to 150 mL of iodine contrast material is one of the disadvantages of this method, making it undesirable for patients with renal insufficiency. Furthermore, as is the case

with MRA, computed tomographic angiography (CTA) provides only anatomic information and has not been shown to predict clinical responses to revascularization [14].

The ability of CTA, MRA, ultrasonography, captopril scintigraphy, and the captopril test to detect IN were recently compared in a meta-analysis of 55 studies of patients referred for the evaluation of renovascular hypertension [15]. CTA and gadolinium-enhanced MRA had the highest diagnostic performance. However, both CTA and gadolinium-enhanced MRA (without phase contrast flow measurements or estimations of pressure gradients) provide only an anatomic diagnosis of atherosclerotic renal artery stenosis.

The diagnostic use of angiographic methods carries a risk of radiocontrast-induced nephrotoxicity and atheroembolism. The best treatment for contrast-induced renal failure is prevention. Preventive measures include the use, if clinically possible, of scanning without radiocontrast agents, particularly in high-risk patients; the use of lower doses of contrast and avoidance of repetitive studies that are closely spaced; avoidance of volume depletion or nonsteroidal anti-inflammatory drugs, both of which can increase renal vasoconstriction; the administration of intravenous saline solution and the antioxidant acetylcysteine; and the use of low or iso-osmolal nonionic contrast agents [16]. The primary benefit of nonionic contrast agents, whether low or iso-osmolal, is seen in high-risk patients such as those with plasma creatinine concentrations greater than 1.5 to 2 mg/dL (132–176 mmol/L), particularly if they are diabetic. In addition, contrast nephropathy among diabetics with renal insufficiency may be much less likely with an iso-osmolal nonionic contrast agent than with low osmolal nonionic agents. The only currently available iso-osmolal nonionic agent, iodixanol, is expensive. Because low-osmolal agents have replaced high-osmolal agents for almost all intravascular radiologic procedures, the choice for clinicians in high-risk patients is largely between low osmolal and iso-osmolal contrast media [17].

The safety and lack of nephrotoxicity of gadolinium-based contrast agents in magnetic resonance (MR) imaging studies for patients with normal or decreased renal function are well established. As a result, among those at risk for radiocontrast-induced nephropathy for whom vascular imaging is required, MR imaging with gadolinium is preferred to computed tomography or conventional arteriography with iodinated contrast media. To minimize possible nephrotoxicity in MR examinations, doses of gadolinium-based contrast agents of more than 0.3 mmol/kg body weight should be avoided. The current practice of using gadolinium-based contrast media for digital subtraction angiography is limited by possible nephrotoxicity and, if the dose is below 0.3 mmol/kg for renal protection, diminished diagnostic image quality.

Among patients with chronic renal failure, the administration of acetylcysteine in combination with saline hydration and a nonionic, low-osmolal contrast agent protected against contrast nephropathy in some studies [18]. The benefit of acetylcysteine appears to be less consistent in lower-risk patients with a lesser degree of renal insufficiency. Because of these discrepancies, the overall prophylactic efficacy of acetylcysteine was assessed in multiple meta-analyses. In a 2004 study, primary analysis was performed among eight randomized controlled trials that enrolled 885 patients. Compared with hydration alone, acetylcysteine plus hydration significantly reduced the risk of developing nephropathy after contrast administration among those with chronic renal insufficiency (RR, 0.41; 95% CI, 0.22–0.79). However, this overall effect must be viewed in the context of the marked variability in individual risk.

The DA-1receptors are particularly prominent in the renal vasculature, renal tubules, mesenteric vasculature, and peripheral vessels. The DA-1 receptor stimulation vasodilates renal and peripheral vessels, causing a decrease in blood pressure and an increase in renal blood flow. Animal testing with fenoldopam has indicated that it is six times more potent than dopamine in its ability to decrease renal vascular resistance; this suggests that it could be a much more selective and potent renal protective agent against any toxin or stimulus that causes renal dysfunction by reducing renal blood flowor increasing renal ischemia. Fenoldopam has been used for patients who were thought to be at the highest risk for contrast-induced nephropathy, and results suggest that fenoldopam may be of distinct benefit to high-risk patients who need intravascular contrast, especially those who may have to receive a large contrast dose, such as patients undergoing renal angiography [19]. Because available data are anecdotal, it is desirable that prospective, randomized trials are conducted to compare the effects of fenoldopam with those of hydration. The many advantages of carbon dioxide angiography for investigation of renal arterial disease include absences of nephrotoxicity and allergic reaction [20].

DIFFERENTIAL DIAGNOSIS

IN and nephroangiosclerosis usually become apparent in men older than 50 years of age who have a history of arterial hypertension and associated metabolic disorders. The decline of renal function in nephroangiosclerosis is slower than IN and is frequently accompanied by mild proteinuria. Patients with systemic atherosclerosis have a high risk of developing atheroembolism with small-vessel thrombosis. Cholesterol atheroembolism is frequently precipitated by aortic manipulation, although it can arise spontaneously. The deterioration of renal function and existence of extrarenal lesions are manifested by

digital gangrene, livedo reticularis, and the presence of hypocomplementemia and blood and urine eosinophilia [21].

Evidence of cholesterol embolization was found in 25% to 30% of patients who died within six months of cardiac catheterization or aortography. In several reports of renal artery angioplasty, cholesterol emboli were present in 0.6% to 6% of patients, an overall incidence of 16 of 1014 attempted dilations. A comprehensive review of noncoronary angioplasty (4662 renal and peripheral cases) reported that the incidence of embolism was 4.8%.

TREATMENT

The aim of treatment is to protect or improve renal function. Specific management in patients with chronic ischemic renovascular diseases such as IN are medical therapy, angioplasty (usually with stent placement), and surgery. Candidates at risk for IN frequently need medical therapy for other manifestations of atherosclerotic disease. Many of the procedures used to reduce mortality related to stroke and coronary disease affect atherosclerotic kidneys [22]. Medical therapy with antihypertensive drugs, particularly ACE-I or AIIRA, can effectively control blood pressure in most patients with bilateral renal artery stenosis. Hypertension can be resistant to antihypertensive therapy; such patients may be candidates for revascularization. Despite adequate control of blood pressure, the chronic administration of an ACE-I (and perhaps other antihypertensive drugs) may also lead to atrophy behind the stenosis and will not prevent progression of the stenotic lesions. In addition to issues related to blood pressure control and progressive renal artery atherosclerosis, these patients are also at risk for extrarenal cardiovascular events. When evaluating therapeutic efficacy, one must remember that the survival rate of elderly, atherosclerotic, and hypertensive patients undergoing dialysis is very low. Revascularization might improve survival by slowing the progression of renal insufficiency or enabling better control of hypertension.

Percutaneous transluminal renal angioplasty (PTRA) with stent is an attractive option, because it is associated with relatively low morbidity and mortality [23]. However, its efficacy is reduced in patients with severe atherosclerosis, especially when the ostium of the renal artery is affected. Because most atheromatous renal artery stenoses are ostial, the response to balloon dilatation may be poor and must be taken into account when PTRA is indicated. PTRA of ostial stenosis is successful in only 50% of cases; the incidence of restenosis ranges from 5% to 38%, and a large proportion of patients experience decreased renal function.

Although consensus has not been reached among investigators, revascularization is indicated in patients with the following characteristics: a decrease in renal artery diameter greater than 75%; progressive deterioration of renal function in individuals with renovascular disease but with satisfactory control of arterial pressure; nonreversible renal insufficiency in the presence of hypotensive drugs (excluding ACE-Is) as a consequence of critical stenosis; a resistive index for duplex Doppler ultrasonography of less than 80; and renal failure caused by aortic, unilateral, or bilateral renal artery thrombosis in which the kidneys remained viable because of collateral circulation. Van Jaasrveld et al [24] randomly assigned 106 patients with hypertension who had atherosclerotic renal-artery stenosis and renal insufficiency to PTRA or drug therapy To be included in the study, patients also had to have a diastolic blood pressure of 95 mm Hg or higher despite treatment with two antihypertensive drugs, or an increase of serum creatinine concentration during treatment with an ACE-I of at least 0.2 mg/dL (20 μmol/L). Blood pressure, doses of antihypertensive drugs, and renal function were assessed at months 3 and 12 of the study, and patency of the renal artery was assessed at month 12. They concluded that, for patients who have IN secondary to atherosclerotic renal artery stenosis with normal or mild impairment of renal function, primary angioplasty was equally or less effective than antihypertensive drugs alone for reducing blood pressure. Nevertheless, "rescue" angioplasty to control refractory hypertension was efficacious. ACE-I renograms have little utility for the management of IN, because they do not predict which patients will respond to therapy.

Self-expanding and balloon-expandable metallic stents [PTRA with stent (PTRAS)], which might improve angioplasty results, immediate post-angioplasty complications, and restenosis, have recently became available for atherosclerotic renal arterial stenosis. The most extensive review to date on the efficacy of PTRA and PTRAS was conducted by Leertouwer et al in 2000 [25]. They included all studies dealing with PTRA (10 articles, 644 patients) and PTRAS (14 articles, 678 patients). The population selected shared similar characteristics: mild-to-moderate renal insufficiency and aged 60 to 75 years. Primary outcome measures were similar (change in renal function or hypertension control, angiographic patency). They concluded that PTRAS is superior to PTRA because of a higher initial success rate and a lower restenosis rate. Stent placement was associated with a significantly lower percentage of patients with improved renal function. However, it is likely that this is because the baseline renal function was better in PTRAS studies. This meta-analysis suggests that 65% to 70% of patients have stable or improved renal function after PTRA/S.

Because of a lack of clear evidence for drawing up definitive guidelines for IN, clinical practice is frequently based on subjective criteria. Further studies in which renal function is documented as the primary outcome are needed. Multicenter, randomized studies are in progress

to determine whether PTRAS improves the cardiovascular morbidity and mortality of patients.

The ASTRAL study will eventually include about 1000 IN patients [26]. Patients with a clinical presentation identified as IN are randomly assigned to PTRA with or without stent placement plus medical care, or to medical care alone. There are no restrictions on medical treatment of patients, but ACE-I/AIIRA will only be used if considered essential, such as in cases of congestive heart failure. The primary outcome is the mean slope of the reciprocal plots of creatinine concentration over time.

The CORAL trial was designed to test the difference in survival free of adverse cardiovascular and renal end points in hypertensive patients [27]. It began in 2004 with a population of about 1000 IN cases and will continue for 5 years. The randomized design compares renal artery stenting plus optimal medical therapy with optimal medical therapy alone. ACE-I cases are not excluded from therapy considered to be standard for the care and management of patients with atherosclerotic disease. The primary end point is a combination of cardiovascular or renal death, stroke, myocardial infarction, hospitalization for congestive heart failure, doubling of serum creatinine, and renal replacement therapy.

Surgery is still the first treatment choice for patients with IN of atherosclerotic origin. The main indications are an aorto-iliac atherosclerotic condition requiring revascularization, severe ostial stenosis, and complete renal artery thrombosis. Traditionally, several criteria have been used for the indication of revascularizing surgery: total kidney size greater than 8 cm; angiographic or scintigraphic demonstration of retrograde filling of the distal renal arterial tree from collateral vessels; patency of the distal end of the renal artery; viability of the involved kidney as shown by isotopic renography; well-preserved tubules and minimally sclerosed glomeruli in a biopsy performed before revascularization. Groups skilled in revascularization surgery reported improvement or stabilization of renal function in 79% to 90% of cases and a progressive decline in 10% to 20% of cases. Surgery-related mortality was 4.6% and was associated with the elderly and with symptoms of congestive heart failure [28].

CONCLUSION

IN is a pathology that is increasing in prevalence and for which early diagnosis is essential to avoid progression to irreversible renal insufficiency. Once the diagnosis has been confirmed, it is essential to evaluate the advantages and risks of potential renal revascularization techniques on an individual basis.

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REFERENCES

1. Jacobson HR: Ischemic renal disease: An overlooked clinical entity. *Kidney Int* 34:729–743, 1988
2. Mailloux LU, Napolitano B, Bellucci AG, *et al*: Renal vascular disease causing end-stage renal disease, incidence, clinical correlates, and outcomes: A 20-year clinical experience. *Am J Kidney Dis* 24:622–629, 1994
3. Connolly JO, Higgins RM, Walters HL, *et al*: Presentation, clinical features and outcome in different patterns of atherosclerotic renovascular disease. *QJM* 87:413–421, 1994
4. Van Ampting JM, Penne EL, Beek FJ, Koomans HA: Prevalence of atherosclerotic renal artery stenosis in patients starting dialysis. *Nephrol Dial Transplant* 18:1147–1151, 2003
5. Valderrabano F, Berthoux FC, Jones EH, Mehls O: Report on management of renal failure in Europe, XXV, 1994 end stage renal disease and dialysis report. The EDTA-ERA Registry. *Nephrol Dial Transplant* 11(Suppl 1):2–21, 1996
6. Fatica RA, Port FK, Young EW: Incidence trends and mortality in end-stage renal disease attributed to renovascular disease in the United States. *Am J Kidney Dis* 37:1184–1190, 2001
7. Alcazar JM, Marin R, Gomez-Campdera F, *et al*: Spanish Group of Ischaemic Nephrology (GEDENI). Clinical characteristics of ischaemic renal disease. *Nephrol Dial Transplant* 16(Suppl 1):74–77, 2001
8. Alcazar JM, Rodicio JL: Ischemic nephropathy: Clinical characteristics and treatment. *Am J Kidney Dis* 36:883–893, 2000
9. Jackson B, McGrath BP, Matthews PG, *et al*: Differential renal function during angiotensin converting enzyme inhibition in renovascular hypertension. *Hypertension* 8:650–654, 1986
10. van de Ven PJ, Beutler JJ, Kaatee R, *et al*: Angiotensin converting enzyme inhibitor-induced renal dysfunction in atherosclerotic renovascular disease. *Kidney Int* 53:986–993, 1998
11. Zalunardo N, Tuttle KR: Atherosclerotic renal artery stenosis: Current status and future directions. *Curr Opin Nephrol Hypertens* 13:613–621, 2004
12. Radermacher J, Chavan A, Bleck J, *et al*: Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. *N Engl J Med* 344:410–417, 2001
13. Tan KT, van Beek EJR, Brown PWG, *et al*: Magnetic resonance angiography for the diagnosis of renal artery stenosis: A meta-analysis. *Clin Radiol* 57:617–624, 2002
14. Schoenberg SO, Rieger J, Nittka M, *et al*: Renal MR angiography: Current debates and developments in imaging of renal artery stenosis. *Semin Ultrasound CT MR* 24:255–267, 2003
15. Boudewijn G, Vasbinder C, Nelemans PJ, *et al*: Diagnostic tests for renal artery stenosis in patients suspected of having renovascular hypertension: A meta-analysis. *Ann Intern Med* 135:410–411, 2001
16. Rudnick MR, Berns JS, Cohen RM, Goldfarb S: Nephrotoxic risks of renal angiography: Contrast media-associated nephrotoxicity and atheroembolism–a critical review. *Am J Kidney Dis* 24:713–727, 1994
17. Asif A, Epstein M: Prevention of radiocontrast-induced nephropathy. *Am J Kidney Dis* 44:12–24, 2004
18. Fishbane S, Durham JH, Marzo K, Rudnick M: N-acetylcysteine in the prevention of radiocontrast-induced nephropathy. *J Am Soc Nephrol* 15:251–260, 2004
19. Hunter DW, Chamsuddin A, Bjarnason H, Kowalik K: Preventing contrast-induced nephropathy with fenoldopam. *Tech Vasc Interv Radiol* 4:53–56, 2001
20. Cronin P, Patel JV, Kessel DO, Robertson I: Carbon dioxide angiography: A simple and safe system of delivery. *Clin Radiol* 60:123–125, 2005
21. Wright JR, Duggal A, Thomas R, Reeve R: Clinicopathological correlation in biopsy-proven atherosclerotic nephropathy: Implications for renal functional outcome in atherosclerotic renovascular disease. *Nephrol Dial Transplant* 16:765–770, 2001
22. Pattison JM, Reidy JF, Rafferty MJ, *et al*: Percutaneous renal angioplasty in patients with renal failure. *Q J Med* 85:883–888, 1992
23. Harden PN, MacLeod MJ, Rodger RS, *et al*: Effect of renal-artery

stenting on progression of renovascular failure. *Lancet* 349:1133–1136, 1997
24. VAN JAARSVELD BC, KRIJNEN P, PIETERMAN H, DERKX FH: The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. Dutch Renal Artery Stenosis Intervention Cooperative Study Group. *N Engl J Med* 342:1007–1014, 2000
25. LEERTOUWER TC, GUSSENHOVEN EJ, BOSCH JL, *et al*: Stent placement for renal arterial stenosis: Where do we stand? A meta-analysis. *Radiology* 216:78–85, 2000
26. THE ASTRAL TRIAL. Available at: http://www.astral.bham.ac.uk. Accessed
27. THE ASTRAL TRIAL. Available at: http://www.clinicaltrials.gov. Accessed
28. TEXTOR SC: Ischemic nephropathy: Where are we now? *J Am Soc Nephrol* 15:1974–1982, 2004